Smallpox Vaccination *Management of Complications*

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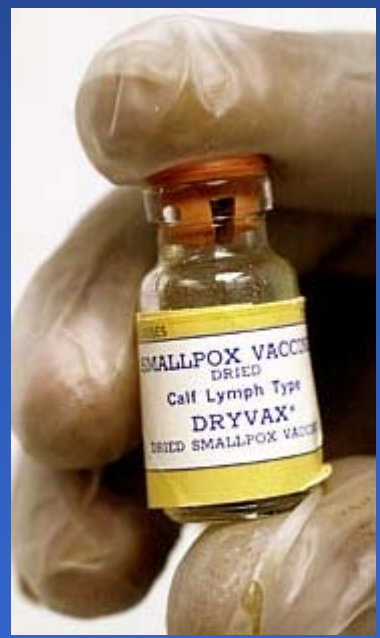
Infectious Diseases

Altru Health System



Objectives

- Describe normal and adverse events that can follow smallpox vaccination (AES).
- Identify laboratory testing useful for evaluating rash illness.
- Review pharmacology related to medical management of AES.
- Describe infection controls for patients with AES including empiric isolation for rash illness.
- List resources to assist with management of AES and rash illness.

About the photo images

www.bt.cdc.gov/training/smallpoxvaccine/reactions/default.htm

Images courtesy of:

- Vincent Fulginiti MD
- The Estate of Henry C. Kempe MD
- NIH/Smallpox Vaccination Dilution Studies
- Centers for Disease Control and Prevention
- New England Journal of Medicine
- Logical Images, Inc

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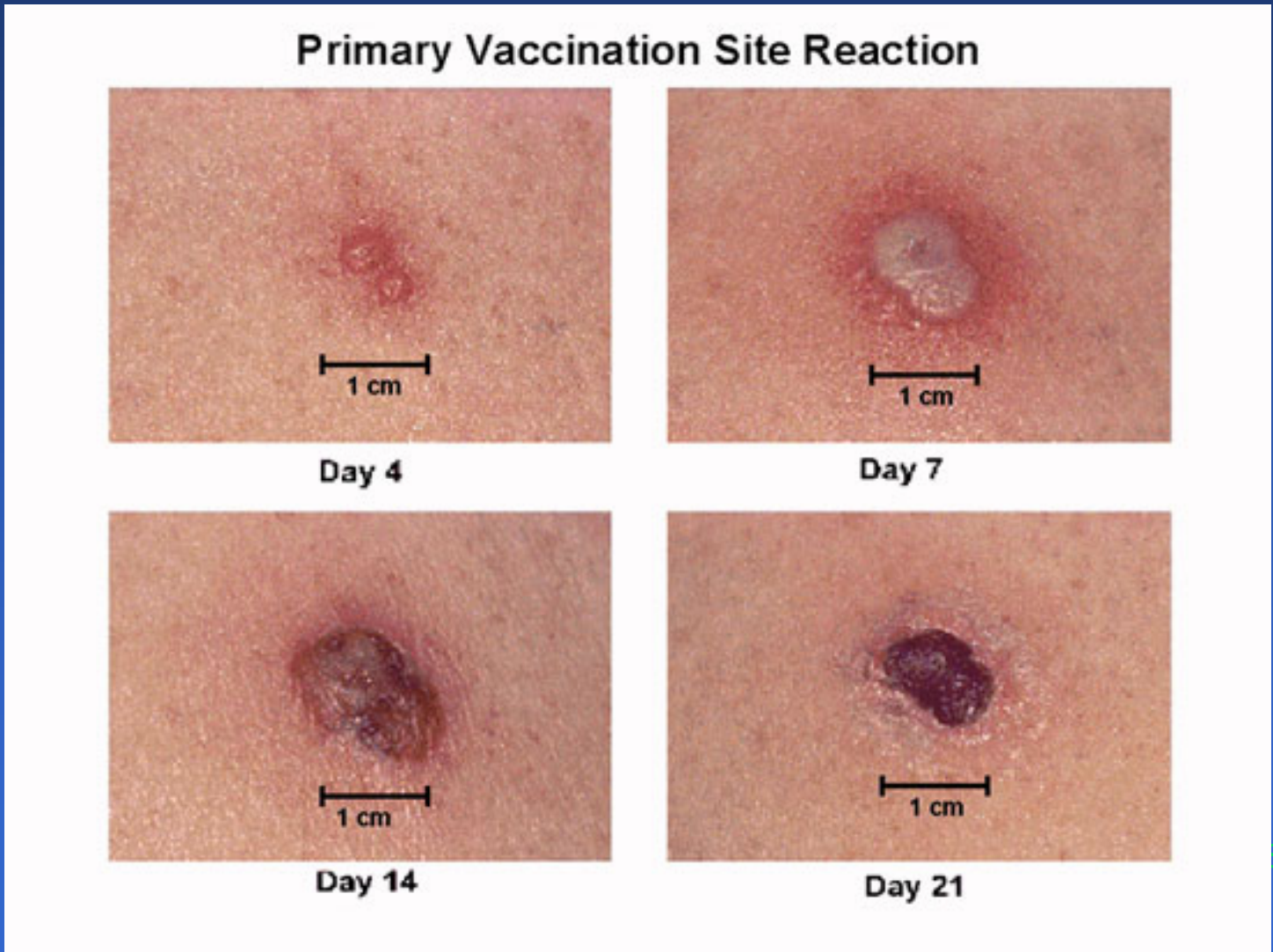
Primary Site Reaction Smallpox Vaccine



Normal Reaction Time

Day	Description
0	vaccination
3-4	papule
5-6	vesicle with erythema
8-9	pustule
12 +	crusting
17 - 21	scar


Source: Logical Images
Day 4 (8-13-02)
Day 6 (8-15-02)
Day 8 (8-17-02)
Day 10 (8-19-02)


Source: Logical Images
Day 12 (8-21-02)
Day 14 (8-23-02)
Day 16 (8-25-02)
Day 18 (8-27-02)
Day 20 (8-29-02)

Normal Systemic Symptoms

- Soreness
- Intense erythema
- Malaise
- Lymphadenopathy (local)
- Myalgia, H/A, chills, nausea
- Fever

Normal Reaction Frequency

Lymphadenopathy	25 – 50%
Myalgia, H/A, chills, etc	0.3 – 37%
Fever > 37.7	2.0 – 16.0%

Normal Reactions: Variants

- Local satellite reactions (2.4 - 6.6%)
- Lymphangitis
- Local edema
- Viral cellulitis
  - intense inflammation surrounding papule
- Treatment: supportive

Normal Variants of Vaccine Reaction

- Local edema at vaccination site
- Lymphangitis
- Regional lymphadenopathy (nonfluctuant)
- Satellite lesions

Local Reactions

- Allergic reactions to bandage and tape adhesives
- Large primary vaccination reactions ("robust primary takes" – RPT)
- Secondary bacterial infection

Allergic reaction

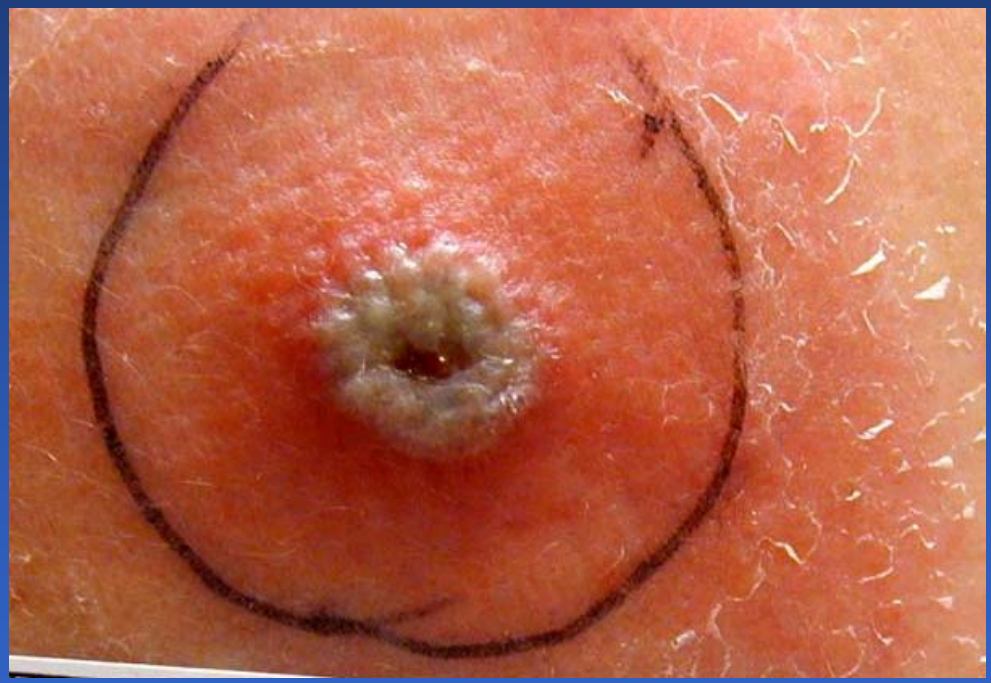
Robust Primary Takes (RPT)

- Normal variant
- >3 inches of erythema with induration, pain, warmth
- Occur in 5%-15%
- Peak at day 8-10
- Resemble bacterial infection

Satellite lesions

Lymphangitis

Viral Cellulitis



Edema

Revaccination

- Typical - pustule @ 6 - 8 days
- Major reaction - more rapid evolution
- Equivocal reaction
  - allergic reaction
  - no reaction

Revaccination

Accidental Administration

- PO, IV or IM
  - **not advised**
- Follow clinically

Accidental Implantation

- Autoinoculation or contact

Accidental Implantation

- **Common**
  - especially with primary vaccinees

Accidental Implantation

- **Infants and children**
- **Susceptible population**
  - eczema
  - skin disorders with open lesions
  - inflammatory eye lesions

Accidental Implantation

- Transfer of virus to another body part
- High viral load

Accidental Implantation - Diagnosis

- **Appears like vaccination unless susceptible patients**
  - eczema vaccinatum, keratitis, etc.
- **Lab not required**

Accidental Implantation
Treatment

- **One or few**
  - supportive
- **Multiple or large area, or toxic**
  - VIG

Inadvertent Inoculation

- Uncomplicated lesions require no therapy, self-limited, resolve in ~3 weeks
- VIG may speed recovery if extensive or painful genital involvement
- **Hand hygiene*** after contact with vaccination site or contaminated material most effective prevention

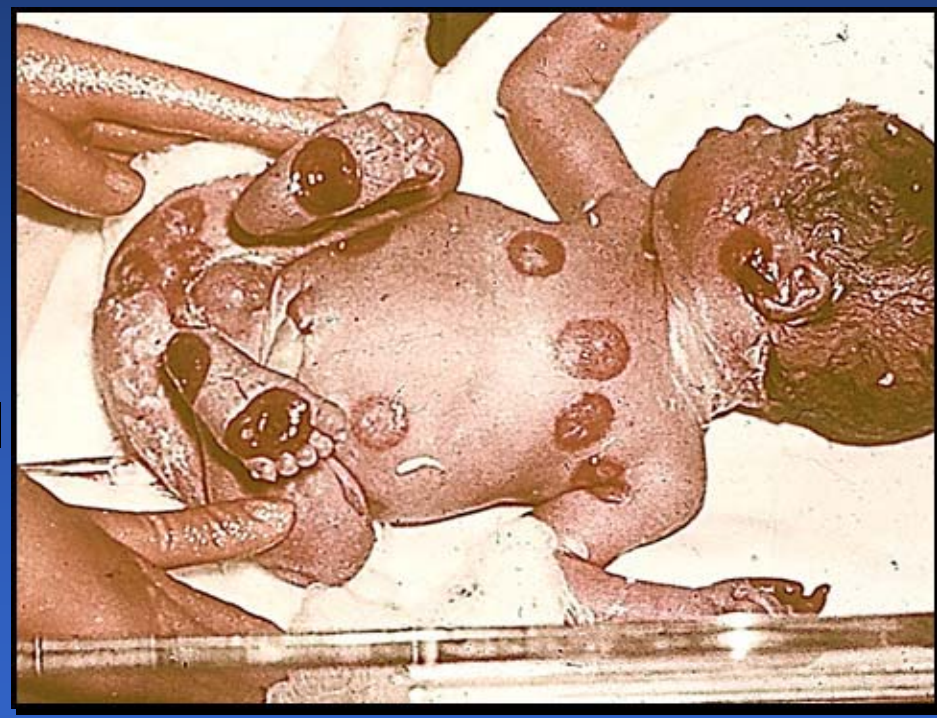
*with soap and water or alcohol hand rub

Secondary Bacterial Infection

- More common among children than adults
- Usually *Staph aureus* or Group A beta hemolytic Streptococci
- Anaerobic and mixed infections may occur
- Evaluate with gram stain and culture
- Antibiotic therapy based on culture

Fetal Vaccinia

- Rare complication (<50 cases reported)
- usually second or third trimester
- Fetal infection - spontaneous abortion Death usually occurs before birth or in perinatal period
- No known congenital malformations
- No known reliable intrauterine diagnostic test



Fetal Vaccinia

- **Clinical**
  - generalized vaccinia
  - progressive vaccinia
- **Diagnosis**
  - H/O vaccination
  - typical lesions
- **Treatment**
  - if viable - VIG

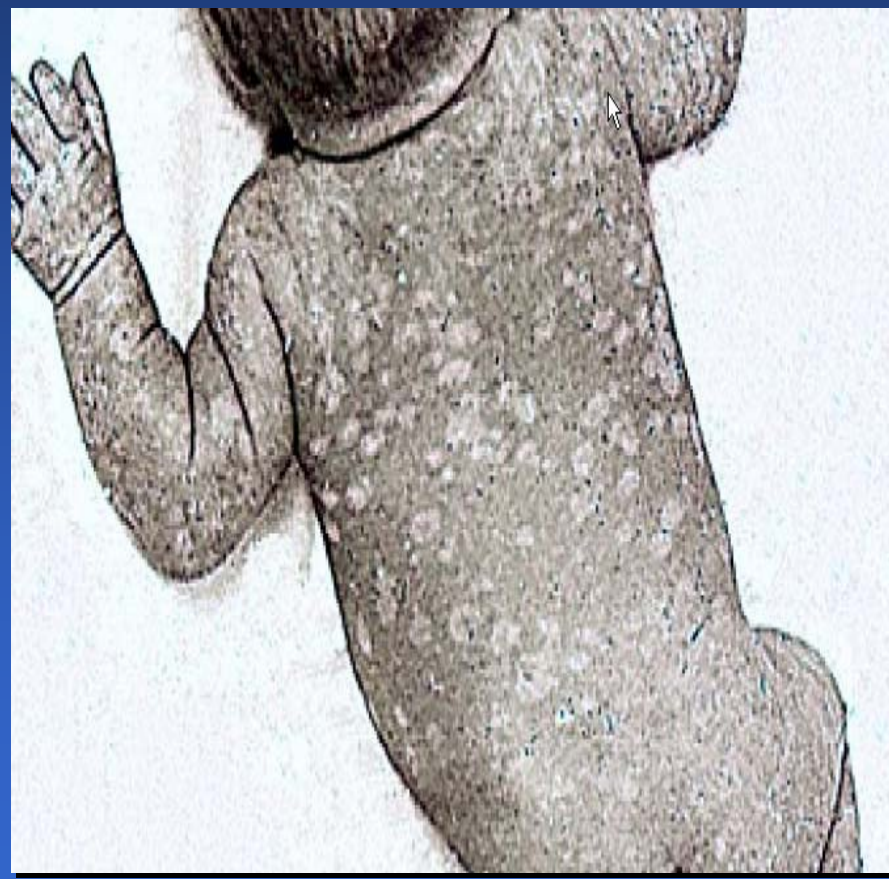


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TABLE 3. RATES OF COMPLICATIONS FROM VACCINIA, ACCORDING TO VACCINATION STATUS AND AGE.*

COMPLICATION	PRIMARY VACCINATION (N=650,000)				REVACCINATION (N=998,000)			
	0–4 YR	5–19 YR	≥20 YR	ALL AGES	1–4 YR†	5–19 YR	≥20 YR	ALL AGES
	no. of events/1 million vaccinations							
Accidental infection	564	371	606	529	198	48	25	42
Generalized vaccinia	263	140	212	242	0	10	9	9
Erythema multiforme	209	87	30	165	73	2	9	10
Eczema vaccinatum	39	35	30	39	0	2	5	3
Postvaccinal encephalitis	15	9	0	12	0	0	5	2
Progressive vaccinia	3	0	0	2	0	0	7	3
Other	222	214	636	266	18	24	55	39

*Data are from a 1968 survey of 10 states.[44] No deaths occurred.

†No children under the age of one year were revaccinated.

Eczema Vaccinatum

- Generalized spread in patient with eczema or true atopic dermatitis, or a history of eczema or atopic dermatitis
- Severity independent of the activity
- Severe cases among contacts

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Eczema Vaccinatum clinical

- Skin lesions may be papular, vesicular, or pustular
- May occur anywhere on the body
- Predilection for areas of previous atopic dermatitis
- Patients often severely ill

Sibling contact

Eczema Vaccinatum clinical

- May resemble septic shock
- Can be lethal
- Bacterial superinfections
- Abscess
- Resolve with extensive scarring

Eczema vaccinatum in contact to recently vaccinated child.

- Recovered without sequelae or permanent ocular damage.

2/3/2003

Eczema Vaccinatum diagnosis

- **Characteristic lesions**
  - H/O vaccine or contact with a vaccinee
- **Lab may be required to differentiate**
  - HSV PCR
- Septic work up

Eczema Vaccinatum treatment

- **Management**
  - Hemodynamic support
  - Meticulous skin care
  - **Early treatment with VIG**
  - Treatment of secondary bacterial or fungal infections as needed
- **Lesions contain vaccinia virus**

Post-Vaccinial Encephalitis

- Usually affects primary vaccinees
- Meningoencephalitis
- Cause unknown - autoimmune theory
- Variety of CNS signs (e.g., ataxia, confusion, paralysis, seizures, or coma)
- 15%-25% die, 25% develop neurological sequelae
- Occurred 3-12 cases per million primary vaccinations

Post-Vaccinial Encephalitis

- Diagnosis of exclusion
  - HSV, EBV, VZV, enterovirus, arbovirus
- CSF may have increased opening pressure, lymphocytosis, elevated protein
- Treatment is supportive
- VIG not effective
- Anticonvulsive therapy and intensive care may be required

Erythema Multiforme

- May present as macules, papules, urticaria, or bulls-eye lesions
- Usually appears within 10 days
- Does not progress
- Does not contain vaccinia virus

Erythema Multiforme

- Increasing frequency @ younger age
  - < 4 - 164 cases/million
  - .20 - 30.3 cases/million
- Most erythematous, pruritic, and benign

Erythema Multiforme

- Mild - few patches and blotches
  - urticaria, vesicles, and/or pustules
- Extensive - most of body
- Severe - Stevens-Johnson Syndrome

Erythema Multiforme
diagnosis

- **Rash**
  - H/O vaccination
- **Vesicles and pustules**
  - Difficult to differentiate
    - generalized vaccinia
    - accidental implantation
    - occurs later
    - devoid of massive erythema
    - may require viral studies

Erythema Multiforme
treatment

- Pruritis - antihistamine
- Skin
  - no special care except
    - Stevens-Johnson
      - hospitalize
- VIG ineffective

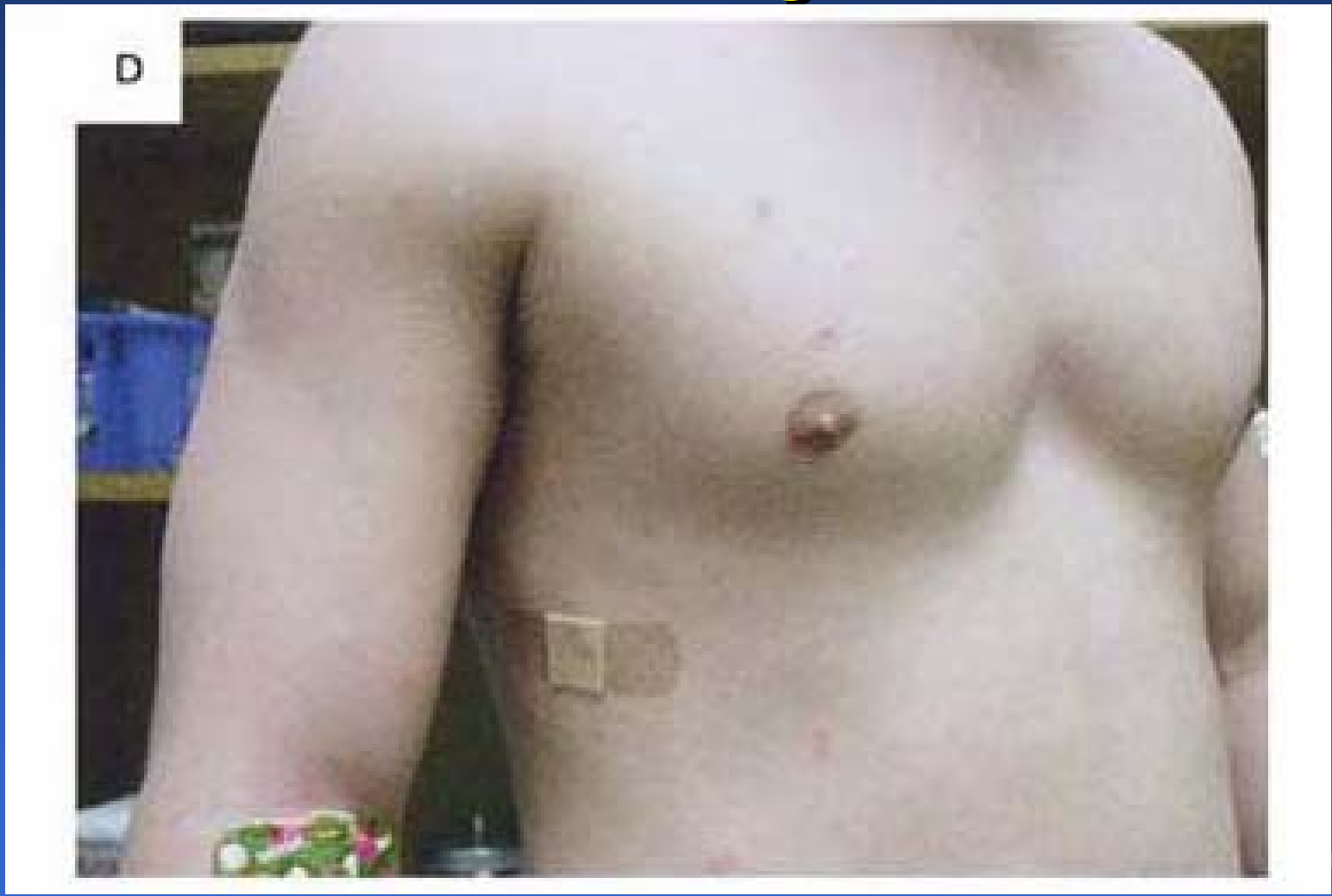
Erythema Multiforme
Ankle, Day 8

Erythema Induration from Pustule to Elbow

Rashes Following Smallpox Vaccine

- Flat, erythematous, macular, or urticarial lesions
- Usually do not become vesicular
- Do not appear to involve viral multiplication or systemic dissemination
- Occur approximately 10 days after vaccination
- Resolve spontaneously within 2 to 4 days

Generalized Vesicular Rash, Day 11



Generalized, Flat, Erythematous Rash, Leg, Day 13

Localized Vesicular Rash on Hands

Localized Papular Rash, Elbow, Day 18

Generalized Vaccinia

- Vesicles or pustules appearing on normal skin distant from the vaccination site
- Often accompanied by fever, headache, and myalgias
- Usually occur 6-9 days after vaccination

Generalized Vaccinia

- Generally benign
- Confused with eczema vaccinatum
- Pathogenesis
  - viremia
  - skin only target
  - ? Humoral defect

Generalized Vaccinia
clinical

- Skin lesion
  - similar to vaccine site except:
    - smaller
    - more rapid evolution
  - any part of the body
  - can be recurrent
    - every 4 - 6 weeks
    - as long as 1 year

Generalized Vaccinia
Differential Diagnosis

- Erythema multiforme
  - not umbilicated
  - doesn't resemble vaccination
- Eczema vaccinatum
  - H/O eczema
  - distribution of eczema

Generalized Vaccinia
Differential Diagnosis

- Inadvertent inoculation at multiple sites
- Early progressive vaccinia
- Disseminated herpes
- Severe varicella
  - superficial vesicles
- Smallpox

Generalized Vaccinia

- Treatment
  - usually none
  - if extensive or recurrent then VIG
  - Work-up humoral defects

Generalized Vaccinia

- Generally self-limited, usually no treatment
- VIG considered for recurrent disease or severe disease
- Lesions contain vaccinia

Progressive Vaccinia

- Often life-threatening
- Other names
  - vaccinia necrosom
  - vaccinia gangrenosa
  - disseminated vaccinia
- Rare (1 / million primary vaccinees)

Progressive Vaccinia

- Primary vaccination does not heal
- Progresses to ulcerative lesion, often with central necrosis
- Little or no inflammation at the site and generally little pain
- Virus continues to spread locally and through viremia

Progressive Vaccinia
Who's susceptible?

- Immunodeficiency
  - esp CMI
- HIV
- Cancer
- Organ transplant
- Immunomodulating drugs

Progressive Vaccinia pathogenesis

- Cell to cell spread
- Necrotic skin centrally
  - advancing edge
- Viremia
  - metastatic skin sites
  - evolve similarly
- Secondary bacteria, fungal, or parasitic (PCP)

Progressive Vaccinia clinical

- Primary vaccine site doesn't heal
- Ulcerative and/or pustular lesions with central necrosis
- Circumferential expansion
- Viremia cause satellite lesions

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Progressive Vaccinia clinical

- No lymphadenopathy
- No splenomegaly
- Extensive tissue destruction
- Superinfections
- Sepsis, DIC
- Unmatched lymphocytes -GVHD

Progressive Vaccinia (vaccinia necrosum) in Patient with Chronic Granulocytic Leukemia

Progressive Vaccinia differential diagnosis

- Severe bacterial infection
  - severe inflammation
  - No H/O CMI
- Smallpox
- Chickenpox
  - lack vaccine site
  - superficial
  - various stages of rash
- Disseminated HSV

2/3/2003

Progressive Vaccinia testing

- Rash and fever algorithm
- Consult Public Health & ID
- HSV PCR
- VZV PCR
- Viral cultures
- Stains
- Immunological work-up
  - HIV, flow cytometry etc

Progressive Vaccinia

- Requires aggressive therapy with VIG
  - up to 10 ml/kg
- Antiviral therapy?
  - Cidofovir
  - Ribavirin
- Surgical debridement?
  - Debulk viral load

Ocular Vaccinia

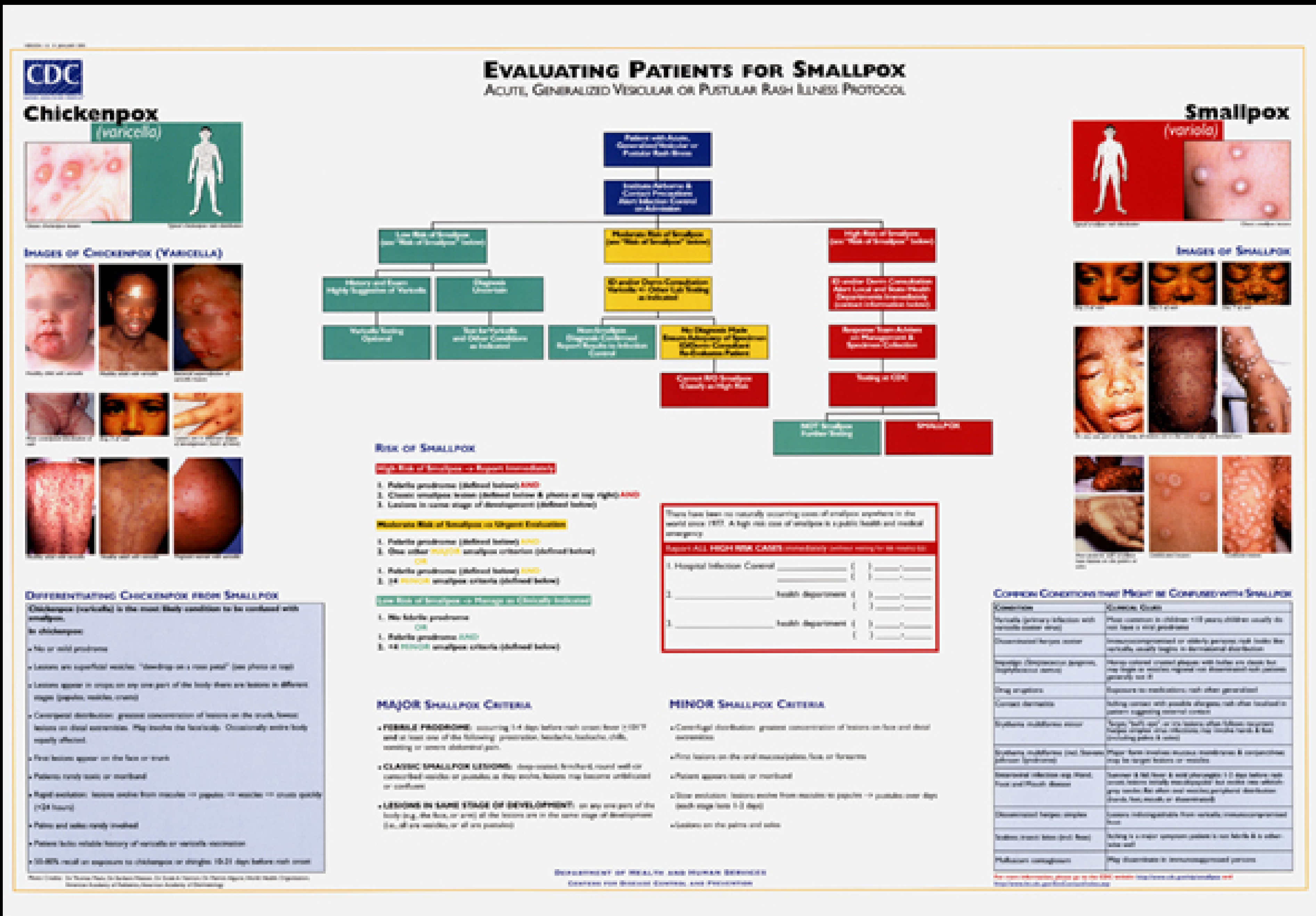
- May present as blepharitis, conjunctivitis, keratitis, iritis, or combination
- Treatment may include topical ophthalmic antiviral agents and VIG

Vaccinia keratitis

- Central grayish, disciform corneal lesion
- Progresses to deeper ring-like structure

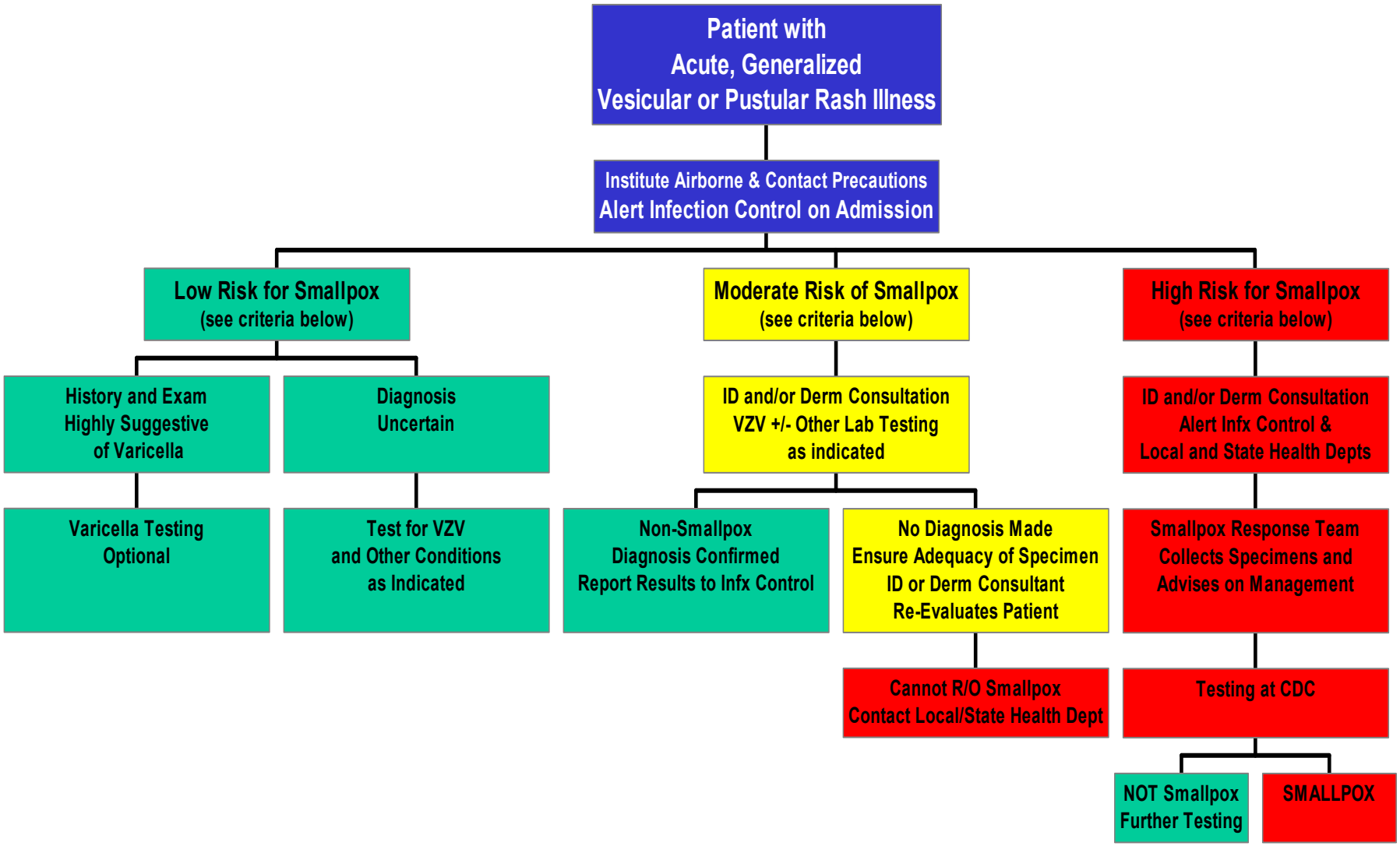
Vaccinia keratitis

- Ophthalmologist referral
- Slit lamp
- Avoid VIG
- Vidarabine
- Trifluridine
- Acyclovir
- Combination antiviral nucleoside + IFN speeds healing



CDC
Evaluating Patients for Smallpox
Acute, Generalized Vesicular or Pustular Rash Illness Protocol
Chickenpox
(varicella)
Smallpox
(variola)
Images of Chickenpox (Varicella)
Images of Smallpox
Risk of Smallpox
Differentiating Chickenpox from Smallpox
MAJOR Smallpox Criteria
MINOR Smallpox Criteria
Common Conditions that Might be Confused with Smallpox
Department of Health and Human Services
Centers for Disease Control and Prevention

Evaluating Patients for Smallpox



Rapid Tests suitable for VSV (smallpox rule-out)

- Tzanck Smear - local cytology lab
- DFA VZV
  - done same day received at NDPHL
- Real time PCR

RULE IN VARICELLA

ND Public Health Lab (NDPHL)

- Contact: **Mike Trythall** or **Bonna Cunningham**
- Phone: **701-328-5262**
- Collection kits/shipping containers -- available within 30 days to NDLRN Level A Laboratories.

  1) DFA Screen for HSV, enterovirus and varicella
     [Touch prep slides in collection kit.]
  2) RT-PCR for vaccinia – send to NDPHL
     [24 hour TAT with consultation.]
  3) Culture [M4 culture transport in collection kit.]
  4) Smallpox confirmation sent to LRN Variola Regional Labs [Contact NDPHL for assistance.]

Sample requirements for Poxvirus DNA

- Lesion “roofs” and crusts
- Vesicular fluids (touch prep)
- Biopsy, autopsy
- 10 ml clot tube; 5 ml EDTA

www.bt.cdc.gov/agent/smallpox/training/webcast/dec2002/files/laboratory-module.ppt
www.bt.cdc.gov/labissues/PackagingInfo.pdf
www.bt.cdc.gov/agents/smallpox/response-plan/files/guide-d.pdf

Lab methods for confirmation of orthopoxvirus diagnostics

- PCR DNA
- Electron microscopy
- Histopathology
- Viral Culture

Vaccinia Immune Globulin

- Immunoglobulin fraction of plasma from persons vaccinated with vaccinia vaccine
- Indications:
  - eczema vaccinatum
  - progressive vaccinia
  - severe generalized vaccinia
- Limitations:
  - no role in smallpox
  - post-vaccinial encephalitis

Vaccinia Immune Globulin
must weigh risk and benefits

- Contraindications
  - Vaccinial keratitis
    - increase scarring in rabbits
  - Serious allergy to human immunoglobulin products
  - Selective IgA deficiency
  - thimerosal allergy
- Pregnancy - category C
- Lactation unknown if in breast milk

Vaccinia Immune Globulin (IV)
adverse effects

- Infusion
  - minimize with slow rate
- moderate toxicity
  - arthralgia, headaches, myalgias, fever, chills, pruritis etc.
- severe toxicity
  - anaphylaxis (IM or IV)
  - renal failure (IV)
  - aseptic meningitis (IV)

Vaccinia Immune Globulin IV formulation

- Refer to package guidelines
- starting dose 0.6 ml/kg = 6000U/kg =100 mg/kg (adult and peds)
- starting infusion rate 0.01 - 0.02 mL/kg/min, gradually increase to 0.08 mL/kg/min
- repeat every 2 - 3 days if needed

Vaccinia Immune Globulin
IM formulation

- Older method, IV should be used first
- Dose
  - 0.6 ml / kg IM
  - Buttock or anterolateral thigh
  - If dose exceeds 10 ml, divide into > 2 sites
  - DO NOT GIVE IV
  - May be repeated if needed

Vaccinia Immune Globulin

- Call state Public Health
- Consult with local ID doctor

Cidofovir (Vistide)

- Nucleotide analogue of cytosine
- Broad spectrum of activity against herpesviruses
- Activity against orthopoxviruses in cell-based and animal models
  - active in vitro against variola
  - active in animals against vaccinia infections
- Currently approved for treatment of CMV retinitis in persons with AIDS
- Available for treatment of vaccinia under IND

Cidofovir Adverse Events

- Renal toxicity
  - Proteinuria
  - irreversible renal failure
- Neutropenia
- Anterior uveitis/iritis
- Metabolic acidosis
- Possible carcinogenicity and teratogenicity
- Probenicid adverse events
  - headache, nausea, vomiting, hypersensitivity, hemolytic anemia, hepatic necrosis, gout, uric acid stones

Cidofovir Indications

- Second line treatment of complications of smallpox vaccination
- Use if patient fails to respond to VIG treatment
- Consult with CDC before use under IND
- Manufacturer recommends use with probenicid

Ribavirin

- IV ribavirin
  - Not commercially available
  - Effective in 1 case of progressive vaccinia

Trifluridine (Viroptic)

- Pyrimidine nucleoside
- indicated HSV keratoconjunctivitis
- pregnancy risk - C
- lactation - unknown if secreted
- adverse reactions:
  - burning, stinging 1 - 10%
  - <1%: hyperemia, edema, keratopathy, keratitis,inc intraocular pressure

Infection Controls

for the patient with adverse event after smallpox vaccination

Reaction	Control
Less serious – normal vaccination varients, few satellite lesions, inadvertant innoculation	Contact Precautions Add Airborne precautions if oral/nasal lesions
Erythema multiforme	Standard Precautions
Vaccinia encephalitis	Contact and Airborne Precautions, until proven vaccina– then Standard
More Serious- generalized vaccinia, eczema vaccinatum, progressive vaccinia, fetal vaccinia	Contact and Airborne Precautions
Keratitis	Contact Precautions
Secondary Bacterial Infection	Contact Precautions

Empiric Isolation

- Screen for history of Smallpox vaccination or contact with vaccinated
  - may be unaware of an inadvertent exposure
- Meningoencephalitis
  - Droplet Isolation
- Vesicular or pustular rash illness
  - Airborne and Contact Isolation

Infection Controls

Contact Isolation

- Standard precautions
- Private room
- Hand hygiene with antimicrobial soap or alcohol
- Gloves
- Gowns
- Dedicated equipment
- Good housekeeping

Airborne Isolation

- Standard precautions
- Negative pressure room
- N95 masks

Infection Control- staffing

For routine assignment, choose HCW in this order
Vaccinated HCW with “take” <3 years. Wear N95 mask.
Hx of prior vaccination and no personal contraindications for smallpox vaccination. Wear N95 mask.
No prior smallpox vaccination and no personal contraindications for smallpox vaccination. Wear N95 mask.
In emergency situations when above not available
HCW with a contraindication in household member only. Scrupulous infection control precautions including N95 mask
HCW with a personal contraindication. Scrupulous infection control precautions including N95 mask

Resources

- www.bt.cdc.gov
- State ND
  - Health Dept 1-800-472-2180
  - Disease Control in Bismarck 701-328-2378
- CDC
  - 770-488-7100 if unable to call State PH
  - Smallpox Clinician Info Line 877-554-4625

Resources

- State Health Officers
  - Terry Dwelle, MD
  - Steve Pickard, MD
- Physicians
  - Shamoon Ahmed, MD
  - Paul Carson, MD
  - James Hargreaves,DO
  - Tze Shien Lo, MD
  - Kent Martin, MD
  - Roberto Patron, MD
  - Vinod Seith, MD
  - Raymond Smego, MD
  - Robert Tight, MD